

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2005/009157

International filing date (day/month/year)
18.03.2005

Priority date (day/month/year)
18.03.2004

International Patent Classification (IPC) or both national classification and IPC
INV. C12Q1/68

Applicant
ADVANDX, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/009157

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☒ in written format
 - ☒ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☒ furnished subsequently to this Authority for the purposes of search.
3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 32-41

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 32-41
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/009157

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:
- ☐ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☒ not paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1-31

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	11-17, 19-29, 31
	No: Claims	1-10, 18, 30
Inventive step (IS)	Yes: Claims	
	No: Claims	1-31
Industrial applicability (IA)	Yes: Claims	1-31
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item IV.

The application lacks unity of invention.

The separate inventions are:

I) Claims 1-31

A method for analysis of a target sequence, comprising contacting the sample with a probe A labeled with a fluorophore which hybridizes to a target sequence, and with a probe B labeled with a quencher which hybridizes to a target sequence adjacent to that of probe A.

II) Claims 32-41

An array comprising a probe immobilized to a surface support.

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

Claim 32 relates to an array comprising a probe (which may be interpreted as DNA, PNA or LNA-containing oligomers); the preferred use stated in the claim does not distinguish subject-matter of the claim therefrom.

A common inventive concept with subject-matter of claim 1, which relates to a method of detection employing a fluorescence/quencher system, is therefore lacking, and the two above defined groups represent independent inventions.

No additional fees were timely paid by the applicant, and an International Search Report has been established for the first invention only. Consequently, the following opinion as well refers to the first invention only.

Re Item V.

1 Reference is made to the following documents:

D1 : YANG M ET AL: "A DNA ASSAY BASED ON FLUORESCENCE RESONANCE ENERGY TRANSFER AND DNATRIPLEX FORMATION" ANALYTICAL BIOCHEMISTRY, ACADEMIC PRESS, SAN DIEGO, CA, US, vol. 259, no. 2, 1 June 1998 (1998-06-01), pages 272-274, XP000780487 ISSN: 0003-2697

- D2 : CARDULLO R A ET AL: "DETECTION OF NUCLEIC ACID HYBRIDIZATION BY NONRADIATIVE FLUORESCENCE RESONANCE ENERGY TRANSFER" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 85, no. 23, 1 December 1988 (1988-12-01), pages 8790-8794, XP000453537 ISSN: 0027-8424
- D3: DEMIDOV V V: "PNA and LNA throw light on DNA" TRENDS IN BIOTECHNOLOGY, ELSEVIER PUBLICATIONS, CAMBRIDGE, GB, vol. 21, no. 1, January 2003 (2003-01), pages 4-7, XP004397629 ISSN: 0167-7799

2 INDEPENDENT CLAIM 1

- 2.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT.

The claim relates to a method of fluorescence reresonance energy transfer (FRET) wherein two probes, labelled with a fluorescent dye (donor) and a quenching moiety (acceptor), respectively, hybridize to adjacent regions.

Such FRET systems are commonly known in the art. D1 and D2, for instance, disclose such systems, wherein the donor probe and the acceptor probe hybridize to adjacent regions on the target nucleic acid. While in D1 and D2, the acceptor moiety is itself a fluorescent dye, it also acts as a quencher for the first dye (explicitely stated in the documents).

The method of claim 1 is therefore not novel in the light of e.g. D1 and D2.

Also, it should be noted that e.g. D1 discloses methods (e.g. for distinguishing between a wild-type and a mutant target allele) wherein the fluorescence of the donor, and the quenching thereof by the acceptor, are assessed and evaluated as hybridization efficiency. The method therein at least in part does not assess the fluorescence of the acceptor. The use of a non-fluorescent quenching moiety instead of the (general) quencher in claim 1 would therefore not be inventive in the light of D1.

3 DEPENDENT CLAIMS 2-31

Dependent claims 2-31 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step (Article 33(2) and (3) PCT).

The use of PNA probes and/or nucleic acid probes comprising LNA (claims 22-28) lacks inventive activity since the use of PNA and LNA in FRET beacons is an alternative to pure DNA probes commonly envisioned and even preferred in the art (see e.g. D3). The skilled person would therefore routinely envision to use such modified probes in the hybridization beacon methods of e.g. D1 or D2.